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Startling facts about emotion in Parkinson's disease: blunted reactivity to aversive stimuli

Dawn Bowers,[1,4] Kimberly Miller,[1,4] Ania Mikos,[1,4] Lindsey Kirsch-Darrow,[1,4] Utaka Springer,[1,4] Hubert Fernandez,[2,4] Kelly Foote[3,4] and Michael Okun[2,4]

[1]Department of Clinical and Health Psychology, [2]Department of Neurology, [3]Department of Neurological Surgery and [4]Movement Disorders Center, McKnight Brain Institute, University of Florida, Gainesville, FL, USA

Correspondence to: Dr Dawn Bowers, Department of Clinical and Health Psychology, PO Box 100165, University of Florida Health Science Center, Gainesville, FL 32610, USA
E-mail: dbowers@phhp.ufl.edu

The amygdala is closely linked to basal ganglia circuitry and plays a key role in danger detection and fear-potentiated startle. Based on recent findings of amygdalar abnormalities in Parkinson's disease, we hypothesized that non-demented patients with this illness would show blunted reactivity during aversive/unpleasant events, as indexed by diminished emotional modulation of the startle eyeblink response. To test this hypothesis, 23 idiopathic patients with Parkinson's disease and 17 controls viewed standardized sets of aversive, pleasant and neutral pictures for 6 s each. During this time, white noise bursts (50 ms, 95 db) were binaurally presented to elicit startle eyeblink responses, measured from electrodes over the orbicularis oculi. After viewing each picture, subjects provided ratings of valence and arousal. The Parkinson's disease patients were in the early to middle stages of their disease, not demented or depressed, and were tested 'on' dopaminergic medication. The two groups were similar in age, education, gender and cognitive screening status. The control group had larger startle responses when viewing negative, aversive pictures than neutral or pleasant pictures. As predicted, startle enhancement during aversive pictures was significantly muted in the Parkinson's disease patients. This blunting was not due to abnormalities in the mechanics of the startle eyeblink *per se*. Nor was it related to depression symptoms, medications (psychotropics), or failure to perceive/appreciate the negative meaning of aversive pictures (i.e. normal valence ratings). Reduced startle reactivity in the disease group was related to disease severity (Hoehn–Yahr) and occurred in the context of reduced arousal ratings of aversive pictures. These findings of blunted startle reactivity add to the literature on emotional changes associated with Parkinson's disease. The basis for this muted reactivity is unknown but may involve an amygdala-based translational defect whereby the results of cognitive appraisal are not appropriately transcoded into somato-motor-arousal responses normally associated with an aversive motivational state. This may arise from faulty dopaminergic gating of the amygdala, resulting in 'inhibition' of the amygdala in the manner described by Marowsky *et al.* (Marowsky A, Yanagawa Y, Obata K, Vogt E. Neuron 2005; 48: 1025–37). More broadly, the findings of muted reactivity to aversive stimuli may reflect a 'bradylimbic' affective disturbance in patients with Parkinson's disease. Future studies are needed to address whether the physiologic blunting observed here might be a useful correlate of apathy.

Keywords: amygdala; depression; dopamine; emotion; psychophysiology; startle

Abbreviations: BDI = Beck Depression Inventory; UPDRS = Unified Parkinson's Disease Rating Scale

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Introduction

Parkinson's disease is a progressive disorder of dopamine depletion involving multiple motor and non-motor circuits of the basal ganglia (Alexander *et al.*, 1986; Mink, 2006). Although the cardinal features of the disease are motor in nature (tremor, rigidity, bradykinesia), changes in mood and emotion are common. Particularly prominent are depression, apathy and anxiety with estimates for depression ranging from 30 to 60% (Cummings, 1992; Slaughter *et al.*, 2001; McDonald *et al.*, 2003). In addition to mood disturbances, blunted facial expressivity and mild deficits in appraising emotional prosody and facial expressions have also been described (Blonder *et al.*, 1989; Borod *et al.*, 1990;

Jacobs *et al.*, 1995; Springelmeyer *et al.*, 1998; Dujardin *et al.*, 2004; Pell and Leonard, 2005; Bowers *et al.*, 2006). The precise mechanisms for these various emotional changes are unknown, but likely relate to neurotransmitter-induced alterations in limbic (i.e. amygdala, ventral striatum, anterior cingulate), cortical, and subcortical regions that are integral parts of the fronto-striatal and mesolimbic circuitry (Alexander *et al.*, 1986).

Recent work in both animals and humans has implicated a limbic-based circuitry, centred on the amygdala that is involved in the generation and modulation of normal fear responses (Davis, 1992, 1993; Ledoux, 2000). This circuitry is responsible for initiating a cascade of behavioural, autonomic and neuroendocrine events which allow for appropriate reactions to threat and danger. One effect of amygdala lesions, both in humans and animals, is abolition or reduction of the fear-potentiated startle response (Angrilli *et al.*, 1996; Bowers *et al.*, 1998; Funayama *et al.*, 2001). The basic startle response itself is a simple protective reflex, mediated at the brainstem level, that serves as a reaction to a potentially harmful or hurtful stimulus (i.e. a loud noise, light flash); behaviourally, the reflex involves rising of the shoulders and sudden eye closure, the startle eyeblink. Importantly, the startle eyeblink response is enhanced when elicited during an aversive context (e.g. watching a scary movie). Amygdalar lesions do not eliminate the startle reflex *per se*, but do abolish priming of the startle response during threatening situations and emotional states (Hitchcock and Davis, 1986, 1991; Rosen *et al.*, 1991). This presumably occurs because the brainstem startle circuitry no longer receives normal input from the central nucleus of the amygdala.

Of particular relevance are reports that the amygdala is affected in patients with Parkinson's disease. In one of the few post-mortem studies that limited cases to non-demented patients with idiopathic Parkinson's disease, Harding *et al.* (2002) found significant reductions in the neuronal density of the basolateral amygdalar group, with the greatest volume loss (i.e. 20%) in the cortical nucleus. Other researchers have reported a 30–45% reduction in amygdalar dopamine agonist binding (Ouchi *et al.*, 1999), increased presynaptic axonal pathology (Bertrand *et al.*, 2003) and increased occurrence of Lewy body pathology (Braak *et al.*, 1994). Still others, using functional imaging techniques, have described *in vivo* alterations of amygdala activation in early-stage Parkinson's disease that seems directly linked to dopaminergic status. In one study, Tessitore *et al.* (2002) tested 10 un-medicated patients with Parkinson's disease during a face–emotion-matching task and found dramatically reduced blood oxygen level dependent responses of the amygdala (and fusiform region). Amygdala activation improved, but did not normalize with dopaminergic medication.

In light of these amygdalar changes, one question is whether patients with Parkinson's disease with the illness respond normally, in terms of physiological reactivity, to aversive situations depicting threat and danger. Because these patients are often facially inexpressive, it can be difficult to determine whether their demeanour 'masks' a normal reaction to emotionally arousing events or whether their physiologic reactions are indeed muted or blunted. To bypass this issue, we used a startle eyeblink task to index emotional reactivity in a group of non-depressed patients with Parkinson's disease. In normal individuals, the size of the startle eyeblink response is directly modulated by emotion (for review, *see* Lang *et al.*, 1998), such that larger startle eyeblink responses occur during aversive, unpleasant emotional contexts than during neutral or pleasant contexts (i.e. negative > neutral > pleasant). To use startle as an index of emotion, it must be shown that the reflexive startle eyeblink itself is reliably elicited. For Parkinson's disease, this appears to be a consistent finding as the amplitude and pattern of muscle recruitment of the basic startle eyeblink responses are similar to controls (Vidailhet *et al.*, 1992). What remains unknown is whether the startle eyeblink of patients with Parkinson's disease is modulated by emotion in the same way as healthy individuals. This question formed the basis for the current study. More broadly, the question speaks to whether Parkinson patients with relatively intact cognitive and psychiatric status would show abnormalities in emotional reactivity.

We modelled our experimental task on one that has been used by Lang and colleagues (Vrana *et al.*, 1988; Bradley *et al.*, 1990). Startle eyeblink responses were elicited by presenting abrupt white noise bursts via headphones to patients and healthy controls while they viewed standardized emotional pictures depicting unpleasant (aversive), pleasant and neutral contents. Startle eyeblink amplitude was measured from electrodes attached under the eye (i.e. over the inferior arc of the orbicularis oculi.) Following each picture, subjective ratings of valence (positive to negative) and arousal were also obtained. Based on observations of amygdalar abnormalities in Parkinson's disease and the relationship between emotion and the amygdala, we hypothesized that patients with Parkinson's disease would show diminished enhancement or priming of the startle eyeblink response during aversive pictures, in the context of normal reactivity during neutral and pleasant pictures.

Material and methods

Participants

Subjects included 23 patients with idiopathic Parkinson's disease and 17 healthy controls. The patients were recruited from the University of Florida Movement Disorders Clinics and the controls were recruited from the community or were spouses of the patients.

We specifically included non-demented patients with Parkinson's disease who were free of major psychiatric disturbance (i.e. major depression or anxiety, no psychotic symptoms, etc.) Informed consent was obtained according to the University of Florida Institutional Review Board guidelines and the Declaration of Helsinki.

Table 1 depicts demographic characteristics of the Parkinson's disease and control groups. As shown, the two groups did not statistically differ in terms of age, education, gender distribution or

Table 1 Demographic and clinical characteristics of subject groups

Characteristics	Parkinson group (n = 23)	Normal controls (n = 17)	*P*-value
Age in years	61.7 (8.1)	58.1 (9.5)	ns
Gender	17 men, 6 women (26% women)	12 men, 5 women (29% women)	ns
Education in years	15.2 (3.4)	13.7 (1.2)	ns
BDI	9.7 (4.2)	4.5 (4.0)	$P < 0.003$
MMSE	28.7 (1.2)	29.1 (1.4)	ns
Duration of Parkinson's disease in years	9.9 (5.9)	—	
Hoehn–Yahr*	2.4 (.44)	—	
UPDRS motor*	22.4 (8.4)	—	
Levodopa equivalent dose	841.7 (371.4)	—	

Note: Means and standard deviations (in parentheses). BDI = Beck Depression Inventory; MMSE = Mini-Mental State Examination, Hoehn–Yahr staging ranges from 0 to 6 (most severe); UPDRS motor = motor scale of Unified Parkinson's Disease Rating Scale; ns = non-significant difference between two groups using independent *t*-test comparisons, or χ^2 (gender distribution).
*Scores obtained from PD patients when they were taking their dopaminergic medications.

cognitive screening status. Overall, the participants were well educated, ranged in age from 39 to 85 years, and were predominantly male (29 men, 11 women). All patients were on dopamine replacement medications and in the early to middle stages of their disease according to standard staging and severity criteria including the Hoehn–Yahr classification (Hoehn and Yahr, 1967) and the motor score of the Unified Parkinson Disease Rating Scale (UPDRS; Fahn *et al.*, 1987). The UPDRS and Hoehn–Yahr staging took place within 6 months of the startle protocol. The patients were tested 'on' their normal dosage of dopaminergic medication. None of the patients met criteria for dementia, based on formal neuropsychological testing, or major depressive disorder or anxiety disorder based on a structured psychiatric interview. On the day of the startle study, all participants were further screened for cognitive and mood status using the Mini Mental State Examination (MMSE; Folstein *et al.*, 1975) and the Beck Depression Inventory (BDI; Beck *et al.*, 1996). The Parkinson's disease group scored significantly higher on the BDI than the controls ($t = 3.24$, $P < 0.003$), although scores of the disease group fell within the non-depressed range (Leentjens *et al.*, 2000; Visser *et al.*, 2006). One patient obtained a score that was mildly elevated (i.e. 15), whereas the remaining Parkinson's disease participants fell below the clinical cut-off for depression. In terms of psychotropic medications, seven patients and one control were taking antidepressants or mixed antidepressant/anxiolytic medications at the time of the startle study. Medications included: Wellbutrin (one PD participant); Effexor (three PD); Celexa (one PD); and Paxil (two PD, one control). No other psychotrophic medications were reported.

Stimuli and procedures

Picture stimuli consisted of 36 pictures (12 positive, 12 negative and 12 neutral) that were selected from the International Affective Picture Set (Lang *et al.*, 2001*a*, *b*) on the basis of normative valence (pleasant/unpleasant) and arousal ratings (from 1 to 9). Regarding content, the unpleasant pictures included mutilations, vicious animals, physical violence, etc. (IAPS nos: 1090, 1300, 2120, 3000, 3010, 3100, 3130, 3530, 6230, 6370, 9040 and 9050), whereas the pleasant set included babies, couples, food and sports activities (IAPS nos: 2080, 2650,4220, 4660, 4680, 5470, 7330, 8030, 8080, 8200, 8370 and 8510). The neutral set included pictures of buildings, office scenes, plants, furniture, etc. (IAPS nos: 2190, 2200, 5500, 7000, 7010, 7030, 7090, 7130, 7170, 7500, 7550 and 7700). In terms of arousal ratings, the pleasant [mean = 6.1 (SD 0.69)] and unpleasant pictures [mean = 6.5 (SD 0.65)] were equivalent in terms of normative ratings, although both were more arousing than neutral pictures [mean = 2.95 (SD 0.54)]. Two different picture orders were created by randomly repositioning the order of the picture blocks.

Testing took place in an electrically shielded and sound-attenuated room in the Cognitive Neuroscience Laboratory of the McKnight Brain Institute. Each trial began with the presentation of a picture, shown for 6 s, on a 20-inch monitor. The participant sat in a reclining chair directly in front of the monitor and wore Telephonics headphones. To elicit a startle eyeblink response, a single 50 ms burst of white noise (95 db, instantaneous rise time) was binaurally delivered through the headphones while the participant viewed each picture. Startle probes were randomly presented at one of three intervals (4200, 5000 or 5800 ms after picture onset) and occurred equally often across each valence category (positive, negative and neutral pictures). Six additional 'filler' pictures (two negative, two neutral and positive) were randomly presented without any probes. Following picture offset, the participants rated each picture.

Prior to beginning the picture viewing task, baseline measures of unprimed startle eyeblink amplitude were obtained by presenting 12 white noise bursts via headphones and measuring blink amplitude. The white noise bursts were randomly delivered at interstimulus intervals ranging from 10 to 18 s. Stimulus presentation, variable inter-trial intervals, and acquisition of physiologic data were synchronized by custom software.

Procedures

The session began with the presentation of the 12 baseline startle stimuli. This was followed by the picture viewing task, which began with two 'filler' trials. Data from the two filler trials were discarded, since they typically reflect initial orienting to the task. Participants were instructed to view the picture on the monitor and disregard occasional noises they might hear. After each picture, participants rated it along the dimensions of valence and arousal using two independent 1–9 ordinal scales. These scales were vertically arrayed on the monitor and depicted versions of a cartoon figure (Self Assessment Manikin: Bradley and Lang, 1994). For valence, the cartoon figure ranged from negative (1) to neutral to positive (9),

and for arousal the figure ranged from sleepy (1) to neutral to highly excited (9). Subjects verbally reported their ratings over an intercom, and these ratings were manually recorded by a research assistant in an adjoining control room. After completion of the subjective ratings, a variable 10–15 s inter-trial interval occurred before onset of the next trial.

Physiologic recordings

Eyeblinks were measured by recording EMG activity from the inferior arc of the orbicularis oculi muscle using Ag-AgCl electrodes. The raw EMG signal was amplified (30 000 gain) and frequencies <90 and >1000 Hz were filtered using Colbourn bioamplifiers. The raw signal was rectified and integrated using a Colbourn Contour following Integrator with a time constant of 200 ms. This information was sent to a Scientific Solutions A/D board interconnected with a computer. Digital sampling at 1000 Hz began 50 ms before presentation of the auditory startle stimulus and continued for 250 ms after startle offset.

Data reduction and analyses

The startle data were reduced offline using custom software that eliminated trials with unstable baselines. Each trial was scored for amplitude (i.e. peak–baseline in millivolts) during the 21–130 ms interval following white noise onset. Trials that failed to reach peak during this interval (i.e. no eyeblink responses) were rejected. Rejections accounted for ~14.2% of all trials and were equally distributed across subjects groups and affect conditions. Each trial was also scored for latency, in milliseconds (ms), between the onset of the white noise burst and the time of the peak amplitude. Average blink amplitude was computed separately for the left and right eyes. Because preliminary analyses revealed no significant differences between left and right eye startle eyeblinks, these two values were averaged and a composite startle eyeblink score was used [i.e. (right blink + left blink)/2] in subsequent analyses.

Results

Baseline startle eyeblink responses

The unprimed startle eyeblink responses during the initial baseline trials were individually examined in terms of average amplitude (in millivolts) and latency (in ms) using separate one-way analyses of variance (ANOVA). Results revealed no difference between the Parkinson's disease and control groups in terms of startle eyeblink amplitude [PD= 700.6 A/D units (SD = 610), controls = 795.6 A/D units (SD 510), $F(1,39) = 0.042$, $P > 0.10$]. Likewise, the latency of the startle response, from onset of the white noise burst to the peak startle amplitude, was also similar for the two groups [PD = 70.1 ms (SD = 17.5), controls = 78.4 ms (SD = 17.4), $F(1,39) = 2.01$, $P > 0.10$]. Thus, the patients displayed baseline startle eyeblink responses that were similar in size and latency to those of the control group.

Affect modulated startle eyeblink responses

Latency

To learn whether startle latency was modulated by valence, a Group (2) × Valence (3) repeated measures ANOVA was performed. Results revealed no significant main effects or interactions (all P's > 0.10). Thus, latency to peak did not appear to vary as a function of group or valence category.

Amplitude

Startle eyeblink responses elicited during the picture task were converted to T-scores (X = 50, SD = 10) following the procedures of Bradley *et al.* (1993) in order to minimize between-subject variability in the absolute size of startle responses. This was done by deriving an overall mean startle amplitude (and standard deviation) from the values of each subject's individual trials. Then, for each participant, average startle responses (T-scores) were computed for the unpleasant, neutral and pleasant pictures and used as the dependent variable in the subsequent analyses.

To test the hypothesis that Parkinson's patients would display diminished startle reactivity during aversive pictures, we conducted a Group (2) × Valence (3) repeated measures analysis of covariance (ANCOVA). Although the two groups did not statistically differ in their overall age or gender distribution, we nevertheless covaried for these factors due to their potential influence on affective psychophysiology. The age covariate approached significance in one condition [Valence × Age linear contrast, $F(1,36) = 3.815$, $P = 0.06$], whereas gender did not. Results otherwise revealed a significant interaction between Group and Valence [$F(2,72) = 7.50$, $P < 0.01$, $\eta_p^2 = 0.172$]. This interaction is depicted in Fig. 1. The control group showed a significant linear trend for valence [i.e. negative > neutral > positive; $F(1,14) = 5.46$, $P < 0.04$, $\eta_p^2 = 0.242$], whereas the Parkinson's disease group did not [$F(1,20) = 0.078$, $P = 0.783$, $\eta_p^2 = 0.004$]. As predicted, startle eyeblink responses of the disease group were significantly smaller in amplitude, relative to controls, during unpleasant, aversive pictures [$F(1,36) = 6.66$, $P < 0.01$, $\eta_p^2 = 0.156$; means: PD = 50.6 (SD = 1.9), control = 52.3 (SD = 1.6)]. There were no significant startle differences between the PD and controls in the pleasant [$F(1,36) = 0.935$, $P > 0.10$, $\eta_p^2 = 0.025$; means: PD = 48.7 (SD = 1.7), control = 48.1 (SD = 2.0)] and neutral picture conditions [$F(1,36) = 1.37$, $P > 0.10$, $\eta_p^2 = 0.037$; means: PD = 50.1 (SD = 2.6), control = 49.1 (SD = 3.0)]. In summary, the control group displayed heightened startle reactivity when viewing aversive/unpleasant pictures, whereas this effect was blunted for the Parkinson's disease patients.

Ratings of affective pictures

One explanation for the attenuated startle effect is that negative pictures were viewed as less aversive or arousing by the Parkinson's disease group. To address this possibility, we examined subjective ratings of the pictures. Table 2 shows the mean valence and arousal ratings across the unpleasant, pleasant and neutral pictures. These ratings were analysed in separate Group (2) × Affect (3) ANCOVAs, using age and gender as covariates. Results of the valence analysis revealed

a significant main effect for Affect [$F(2,72) = 8.94$, $P < 0.001$, $\eta_p^2 = 0.383$]. Both the Parkinson's disease and the control groups rated the pictures with unpleasant contents as more negative than the neutral pictures ($t = 11.3$, $P < 0.001$). In turn, neutral pictures were rated as more negative than pleasant pictures ($t = 14.9$, $P < 0.001$). There were no differences between the disease and control groups in these valence ratings (i.e. non-significant Group effect [$F(1,36) = 0.312$, $P > 0.10$] and non-significant Group × Affect interaction [$F(2,72) = 1.07$, $P > 0.10$].

For arousal ratings, a significant main effect for Affect [$F(2,72) = 4.11$, $P < 0.02$, $\eta_p^2 = 0.125$] occurred. As expected, both types of emotional pictures (pleasant, unpleasant) were rated as more arousing than the neutral pictures [mean pleasant = 5.80 (SD = 1.45), mean unpleasant = 5.85 (SD 1.86), mean neutral = 2.97 (SD = 1.35); pleasant versus neutral: $t = 13.7$, $P < 0.001$; unpleasant versus neutral: $t = 6.94$, $P < 0.001$]. There were no differences in arousal ratings between the pleasant and unpleasant pictures ($t = 0.563$, $P > 0.10$). As shown in Table 2, the main effect for Affect was moderated by a Group × Affect interaction [$F(2,72) = 4.85$, $P < 0.01$, $\eta_p^2 = 0.125$]. *Post hoc* comparisons indicated that the PD patients rated the unpleasant/aversive pictures as less arousing than the controls [$F(1,36) = 4.52$, $P < 0.04$, $\eta_p^2 = 0.117$]. The two groups did not differ in their arousal ratings of neutral [$F(1,36) = 2.68$, $P > 0.10$, $\eta_p^2 = 0.063$] or pleasant pictures [$F(1,36) = 0.109$, $P > 0.10$, $\eta_p^2 = 0.003$].

In summary, the primary results from the rating analyses indicate that the Parkinson's disease patients and control group rated the affective pictures similarly in terms of pleasantness/unpleasantness. However, the patients found the aversive pictures significantly less arousing than did the controls. This was a valence specific effect, since equally arousing pleasant stimuli were rated similarly by the patient and control groups.

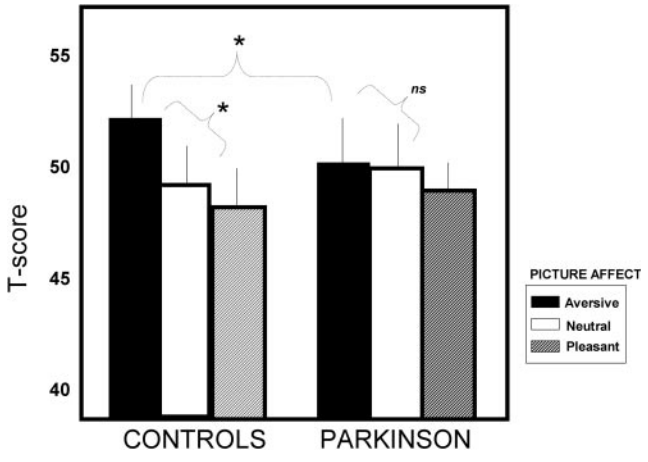

Fig. 1 Peak amplitude (*T*-score) of startle eyeblink responses during aversive, neutral, and pleasant pictures by Parkinson and control groups. Errors bars represent standard deviations. Asterisks refers to significance at $P < 0.05$ level; ns = not significant ($P > 0.10$).

Influence of depression, medication and disease severity and duration

To learn whether the observed startle difference between the Parkinson's disease and control groups was due to depression symptoms, we computed within-group bivariate correlations (Pearson) between scores on the BDI and startle reactivity. To index startle reactivity, we computed difference scores between startle amplitudes (*T*-score) during the negative versus neutral picture condition and used this startle difference value in the correlation analyses. For both groups, none of the BDI-startle correlations were significant (all *P*'s > 0.10, PD: $r = -0.030$, $P = 0.893$; controls: $r = -0.340$, $P = 0.182$; combined: $r = -0.023$, $P > 0.892$). Thus, the presence of self-endorsed depression symptoms was unrelated to startle reactivity.

We also examined the influence of psychotropic medications on startle modulation, as several reports have indicated that antidepressants (especially SSRIs) and anxiolytics may dampen startle reactivity in normal individuals (Davis and Gallagher, 1988; Harmer *et al.*, 2004, 2006). To do so, we identified all individuals who were currently taking antidepressant and/or anti-anxiety medications, removed them from the dataset, and re-examined startle reactivity using the same Group × Valence ANCOVA previously used with the entire sample. Eight individuals (seven PD, one control) were eliminated. This resulted in a sub-sample of 16 patients and 16 controls, who were free of psychotropic medications. The mean age and gender distribution of the newly formed groups were as follows: PD = 13 males and 3 females with a

Table 2 Valence and arousal ratings of affective pictures

Pictures	Valence ratings*			Arousal ratings†		
	Parkinson (n =22)	Controls (n =16)	*P*-value	Parkinson (n =22)	Controls (n =16)	*P*-value
Unpleasant/aversive	2.4 (1.3)	2.4 (0.8)	ns	5.2 (1.9)	6.4 (1.6)	$P < 0.05$
Neutral pictures	4.6 (0.8)	5.0 (0.4)	ns	3.1 (1.4)	2.9 (1.3)	ns
Pleasant pictures	7.2 (0.7)	7.1 (0.8)	ns	6.1 (1.2)	5.5 (1.6)	ns

Means and standard deviations (in parentheses). Means are adjusted for covariates of age and gender; ns = non-significant difference between two groups using independent *t*-test comparisons (Bonferroni corrected).
*Valence ratings: 1–9 Likert scale; 1 is most negative and 9 is most positive.
†Arousal ratings: 1–9 Likert scale; 1 is lowest arousal and 9 is highest arousal.

mean age of 61.4 years (SD 4.5); controls = 11 males and 5 females with a mean age of 59.3 years (SD 9.8). The ANCOVA results were similar to the previously obtained findings with the entire subject sample. As before, the Group × Valence interaction reflected a significant linear effect [$F(2,56) = 5.07$, $P < 0.03$, $\eta_p^2 = 0.153$]. Decomposition of this interaction revealed that startle amplitude to aversive pictures was significantly smaller for the Parkinson's disease group than the controls [$F(1,28) = 4.43$, $P < 0.04$; PD = 50.2 (SD = 1.4), control = 52.4 (SD = 1.8)]. There were no group differences in startle amplitude for neutral or pleasant pictures [neutral pictures: $F(1,28) = 0.337$, $P > 0.10$; PD = 49.5 (SD = 1.41), control = 48.9 (SD = 3.1); pleasant pictures: $F(1,28) = 1.7$, $P > 0.10$]; PD = 48.9 (SD = 1.6). control = 48.1 (SD = 2.1). Thus, diminished startle reactivity to negative pictures was maintained even when membership in the Parkinson's disease group (and control) was strictly limited to individuals who were not taking antidepressants or anti-anxiety medications.

Finally, we examined the relationship among startle reactivity (i.e. difference in startle *T*-scores between negative and neutral conditions), disease severity (UPDRS, Hoehn–Yahr, disease duration) and levodopa equivalent medication among the Parkinson's disease patients. In terms of dopaminergic medications, there was no correlation between levodopa equivalent dosage and startle reactivity (i.e. $r = -0.219$, $P = 0.382$). In terms of disease severity, startle reactivity was inversely correlated with Hoehn–Yahr staging ($r = -0.511$, $P < 0.001$); this means that higher Hoehn–Yahr scores (i.e. worse disease severity) were associated with diminished startle modulation by aversive pictures. A similar pattern was noted, at the trend level, for the UPDRS motor 'on medication' score ($r = -0.390$, $P = 0.089$). Duration of disease was not associated with startle reactivity, although it was correlated with Hoehn–Yahr staging (UPDRS-Hoehn Yahr: $r = 0.515$ $P < 0.02$). To more fully determine the contribution of disease severity factors to startle reactivity, we conducted a series of hierarchical linear regressions analyses. When the Hoehn–Yahr staging was regressed on the startle difference score, the resulting model was significant [$F(1,22) = 6.72$, $P < 0.01$] and yielded a multiple R of 0.511. Thus 22.3% of the variance in startle reactivity was accounted for by disease severity as indexed by Hoehn–Yahr staging. This relationship is depicted in Fig. 2. Adding terms of age and UPDRS motor score did not significantly improve the model fit, although the percentage of variance accounted for increased to 32.5%.

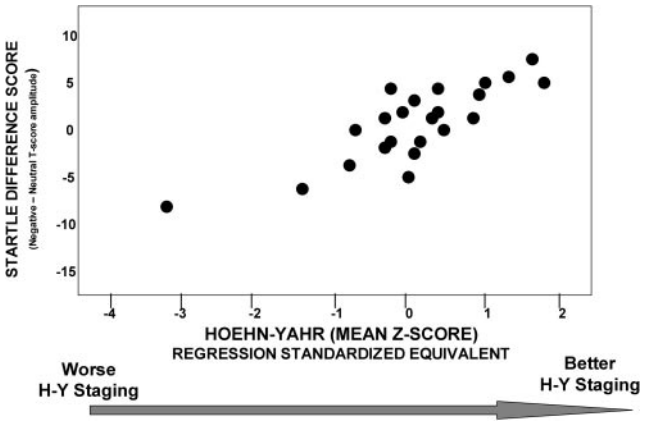

Fig. 2 Regression showing relationship between startle reactivity and Parkinson's disease severity as indexed by Hoehn–Yahr (H–Y) staging. H–Y scores have been normalized. Startle difference score reflects difference in startle amplitude *T*-score between aversive/negative and neutral picture viewing conditions. Larger startle difference scores reflect greater reactivity to unpleasant/aversive pictures.

Discussion

The key finding of this study was that Parkinson's disease patients responded abnormally, in terms of startle reactivity, to aversive pictures depicting threat and unpleasant contents. While the control group showed the typical linear profile of emotion-modulated startle (i.e. negative > neutral > positive), the Parkinson's disease patients did not. Instead, their startle eyeblink responses during negative pictures were significantly muted (i.e. a valence specific startle hypo-reactivity). The attenuated startle profile of the Parkinson's disease group was unrelated to depression. Although the average BDI score of the patient group ($X = 9.7$) was significantly higher than that of the controls ($X = 4.5$), it nevertheless fell below the recommended clinical cut-off (approximate range 13–14) for depression in Parkinson's disease (Leentjens *et al.*, 2000; Visser *et al.*, 2006). Moreover, there was no correlation between startle reactivity and BDI scores. Turning to the research literature, although severe depression (i.e. BDI scores >30) has been associated with lack of affective startle modulation, individuals with mild to moderate depression display normal modulation patterns (Allen *et al.*, 1999; Kaviani *et al.*, 2004). Thus, depression symptoms do not appear to explain the pattern of startle reactivity in the patients.

There are several explanations for the startle hypo-reactivity observed in the patient group. First, the basic startle eyeblink response itself might be aberrant due to compromise of the brainstem reflex circuitry. This is unlikely given that both the latency and the amplitude of the unprimed startle eyeblink were similar for the patient and control groups. Moreover, there were no differences in the percentage of trials on which blinks failed to occur. Our findings correspond to other reports of normal amplitude of startle eyeblink in non-demented patients with Parkinson's disease. Although some authors (Vidailhet *et al.*, 1992; Kofler *et al.*, 2001) have described slowed latency of the startle eyeblink (which we did not observe), we know of no reports of reduced startle amplitude in non-demented patients with Parkinson's disease.

A second explanation for blunted startle reactivity is that the Parkinson's disease patients failed to appropriately

appraise the threat value of the negative pictures and thus did not develop an aversive emotional set. Pictures and scenes are complex visual stimuli whose emotional–semantic meaning is extracted through progressive cortical analyses involving widespread association areas (Blonder *et al.*, 1991; Bradley *et al.*, 2003). Inadequate threat appraisal could be due to visuoperceptual deficits, or because the Parkinson's disease group failed to derive emotional–semantic meaning from the complex pictures they viewed. This possibility was addressed by examining the verbal ratings of valence (positive/negative) and arousal that were made by participants after they viewed each picture. In brief, the Parkinson's disease group rated the unpleasant pictures as equally aversive/negative as the controls. It is possible that the patients rated the pictures based on their normative value (i.e. how they should make someone feel), rather than how they personally felt. This seems unlikely given that the Parkinson's disease group judged these very same unpleasant pictures as less arousing than the controls. Virtually identical findings have been reported by Wieser *et al.* (2006) in an ERP study of Parkinson's disease patients who also rated IAPS pictures for valence and arousal. Taken together, our data suggest that the Parkinson's disease patients in our study recognized the negative/positive meaning of the pictures they viewed and at the same time were aware, based on their arousal ratings, that the negative pictures were less impacting or arousing. What this implies is that the neural systems involved in the cognitive appraisal of affective significance were adequate for extracting the basic dimensions of negative/positive.

A third possibility for the blunted startle reactivity is that the Parkinson's disease patients had a deficit in 'translating' the results of cognitive appraisal into somato-motor, arousal, and other changes that are associated with an aversive motivational state. In this view, cognitive appraisal is intact, but the outputs of this appraisal are insufficient to induce a transient motivational set. Although it is not known which regions are involved in this transcoding process, the amygdala is an ideal candidate due to its location within a complex system linking sensory, limbic/striatal, and higher cortical regions. Converging evidence over the past three decades points to distinct divisions within the primate amygdala including the basolateral complex and the central nucleus (Amaral *et al.*, 1992). The basolateral complex, including the lateral nucleus, is the major afferent input station of the amygdala, being richly innervated by neocortical and subcortical sensory regions. The central nucleus, on the other hand, is a major output station with subcortically directed projections to the hypothalamus and brainstem. Some have proposed that the primary role of the basolateral complex in threat is the evaluation of sensory information along the dimensions of valence, novelty and arousal (Davis and Whalen, 2001; Rosen and Donley, 2006). In this view, evaluation of affective attributes (valence, arousal) is performed within the intrinsic circuitry of the amygdala. An alternative view, and one we support, is that a greater role in affective appraisal is played, at least in humans, by cortical regions (especially prefrontal) that are closely linked to and modulate the amygdala's response to emotion. The deficits in startle modulation observed in the Parkinson's disease patients arise not because of failure to analyse affective significance, but because the amygdala is unable to effectively transcode the results of this appraisal into somato-motor-arousal responses.

How might this occur? Increasing evidence from the basic neurosciences implicates a dopaminergic gating mechanism via which prefrontal cortical regions modulate the amygdala (Royer *et al.*, 1999; Marowsky *et al.*, 2005). Normally, the amygdala is under inhibitory control from the cortex due to activity of local GABAergic interneurons (Lang and Pare, 1998; Rosenkranz and Grace, 1999, 2002; Quirk *et al.*, 2003). This inhibition is disrupted or disinhibited during heightened emotional states possibly due to dopamine release (Inglis and Moghaddam, 1999). In an elegant series of studies with transgenic mice, Marowsky *et al.* (2005) identified a cellular substrate for dopamine-induced disinhibition of the basolateral and central amygdala. This substrate consists of a network of interneurons (parafascular cells; PFC) surrounding the basolateral amygdala that normally inhibit the basolateral group. The PFC interneurons are innervated by projections from the frontal cortex and the mesolimbic region. Marowsky *et al.* (2005) showed that the feed-forward inhibition provided by the PFC interneurons is suppressed by dopamine acting on D1 receptors. This suppression 'disinhibits' both the basolateral and central amygdala. Conversely, blocking of dopaminergic activity resulted in continued inhibition and less amygdala-related reactivity. Thus, dopamine acts as a switch between cortically controlled and disinhibited states of the amygdala.

Turning to Parkinson's disease, one might be tempted to speculate that the disease-related dopaminergic depletion, characteristic of this disorder, would minimize the extent to which the amygdala becomes 'disinhibited' during situations of threat or danger. This, in turn, would result in diminished threat-related startle reactivity, decreased central and autonomic arousal to threat, and decreased neuroendocrine (i.e. cortisol) responses to threat. Such would occur because of diminished amygdalar outflow to the brainstem startle circuitry, the hypothalamus (which mediates sympathetic arousal), and the cholinergic-rich basal forebrain which projects diffusely to and activates the cortex (Amaral *et al.*, 1992). The findings of attenuated startle reactivity and decreased subjective arousal ratings to aversive pictures by the patients are certainly consistent with the amygdala inhibition view.

Our study is the first to report changes in emotional reactivity using a startle modulation task in Parkinson's disease group patients with Parkinson's disease. Previous studies of emotion in Parkinson's disease have been of two general types. In one, the primary focus has been the 'cold' information processing of affective signals, particularly facial

expressions or emotional prosody. Many studies, including those from our laboratory (Jacobs *et al.*, 1995), have found mild deficits on facial emotion perceptual tasks. This has not been universal, however (*see* Adolphs *et al.*, 1998; Tessitore *et al.*, 2002). It is important to recognize that attentional, perceptual and executive deficits that characterize the typical neurocognitive profile of non-demented patients (Zgaljardic *et al.*, 2003; Levin and Katzan, 2005) can disrupt performance on lengthy rating, matching or discrimination tasks with affective stimuli. Thus, disentangling cognitive from true emotional deficits is an important challenge in these types of studies. A second line of research has focused on neuropsychiatric co-morbidities of Parkinson's disease, particularly depression and apathy. These have included prevalence, phenomenology, the extent to which these co-morbidities are biologically based, and how they might be treated (for review, *see* Edwards *et al.*, 2002). Our current findings suggest that, in addition, patients with idiopathic Parkinson's disease may respond less potently, as indexed by startle reactivity, to aversive threatening stimuli. This muted responsivity may relate to increased inhibition of the amygdala secondary to dopaminergic dysfunction. It also occurs in the context of an interesting paradox. Although the patients fully recognized the negative meaning of the aversive pictures, their ratings indicated that they were not fully aroused by these same pictures. Possibly this valence specific hypoarousal stemmed from decreased amygdalar input into the cholinergic-rich basal forebrain, which broadly activates the entire cortical mantle. Importantly, the decoupling between valence and arousal ratings was specific for aversive pictures and did not occur with intense pleasant pictures. This implies that the patients were not pervasively hypo-aroused and/or did not have a cognitive response bias (i.e. tendency to rate everything as low arousal). Similar decoupling between valence and arousal ratings of unpleasant IAPS pictures has been described by other researchers as well (Wieser *et al.*, 2006).

There are several limitations to our study. Although our Parkinson's disease group was relatively homogeneous, they were highly educated (average of 3 years of college) and predominantly male (2:1 ratio). We would not expect education status to play a key role in emotion modulation of startle, although gender differences are likely. In a study of young healthy adults, women responded with greater defensive reactivity to aversive pictures, regardless of specific content, whereas increased appetitive activation was apparent for men when viewing erotica (Bradley *et al.*, 2001). Thus, future studies should be sufficiently powered to examine for gender differences among patients with Parkinson's disease. A second limitation is that we tested patients when they were 'on' their normal dopaminergic medication. The 'on medication' state reflects their optimal performance. In order to obtain a more realistic view of the impact of disease severity, it would be important to evaluate patients in the hypodopaminergic state. This would also provide a stronger test of the amygdala tone hypothesis. We suspect that the blunted startle reactivity observed in the current study would become even more pronounced when the patients are tested off medications. A more serious limitation concerns the impact of medications on startle reactivity. All patients were taking dopaminergic medications (either levodopa or dopamine agonists) and approximately one-third were taking antidepressants (or those with mixed antidepressant/anti-anxiety effects). There are several reports that antidepressants (i.e. serotonin reuptake inhibitors) and anxiolytic medications may dampen startle reactivity in normal adults (Davis and Gallagher, 1988; Harmer *et al.*, 2004, 2006). Because of this issue, we removed the subgroup of participants who were taking any psychotropic medications (seven PD and one control) and re-analysed the startle data. The results were no different from the entire sample. Thus, it does not appear that mood altering medication usage by the current sample of patients was contributory to the results. A final limitation pertains to the extent of disease severity in our Parkinson's disease group. We found that diminished startle reactivity during aversive pictures was associated with increased disease severity, as indexed by Hoehn–Yahr staging (and UPDRS at a trend level). Because disease severity was somewhat restricted (i.e. ranging from 2.0 to 3.5 Hoehn–Yahr), future studies should evaluate a broader spectrum of disease severity in order to more carefully examine this relationship.

In summary, our findings of attenuated startle reactivity to aversive stimuli add to the growing literature on emotional changes associated with Parkinson's disease. The blunting we observed was not due to abnormalities in the mechanics of the startle eyeblink *per se*. Nor was it related to depression symptoms, medications (psychotrophics), or failure to perceive/appreciate the negative meaning of aversive pictures. Rather we propose that this muting may reflect an amygdala-based translational defect whereby the results of cognitive appraisal are not appropriately transcoded into somato-motor-arousal responses normally associated with an aversive motivational state. How this might occur is unknown, but one possible mechanism involves faulty dopaminergic gating of the amygdala, resulting in increased 'inhibition' of the amygdala in the manner described by Marowsky *et al.* (2005). One important question pertains to the broader implications of our findings of muted reactivity, particularly since they occurred in patients who were relatively intact in terms of cognitive and psychiatric status. A growing literature suggests that the apathy variant of depression may be among the primary neuropsychiatric signatures of Parkinson's disease (Isella *et al.*, 2002; Pluck and Brown, 2002; Kirsch-Darrow *et al.*, 2006). Although we did not measure apathy in this study, an obvious question is whether the physiologic blunting, or 'bradylimbia', observed in our Parkinson's disease group might be an early correlate of apathy. Future studies will be needed to address this important question.

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